Drug Interactions: What Do We Know about Non-CYP Drug Metabolizing Enzymes and Transporters?

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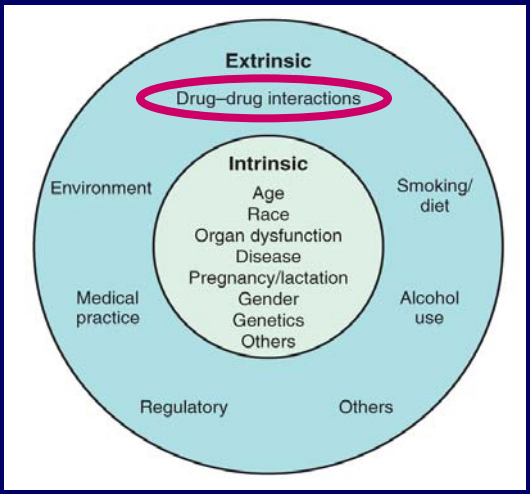
The views presented in this presentation do not necessarily reflect those of the FDA.

Factors Affecting Drug Exposure/Response



Huang S-M, Temple R, Is this the Drug or Dose for you? Clin Pharmacol Ther 84: 287-294, 2008

FDA Clinical Pharmacology guidance documents: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm

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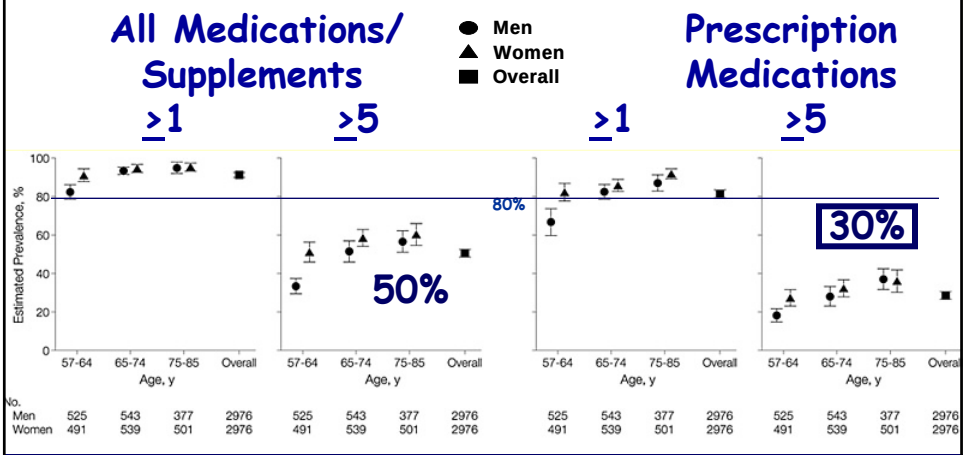
Use of Prescription/OTC/Supplements



Adapted from Qato DM, et al, JAMA 2008; 300:2867-2878.

Drugs Withdrawn from the US Market due to Safety Reasons

Withdrawn	Approv	Drug name	Use	Risk
1998	1997	Mibefradil	High blood pressure/Chronic stable angina	Torsades de Pointes; Drug-drug interactions
1998	1997	Bromfenac	NSAID	Acute liver failure
1998	1985	Terfenadine	Antihistamine	Torsades de Pointes; Drug-drug interactions
1999	1988	Astemizole	Antihistamine	Torsades de Pointes; Drug-drug interactions
1999	1997	Grepafloxacin	Antibiotics	Torsades de Pointes
2000(2002)*		Alosetron*	Irritable bowel syndrome in women	Ischemic colitis; complications of constipation
2000	1993	Cisapride	Heartburn	Torsades de Pointes; Drug-drug interactions
2000	1997	Troglitazone	Diabetes	Acute liver failure
2001	1997	Cerivastatin	Cholesterol lowering	Rhabdomyolysis; Drug-drug interactions
2001	1999	Rapacuronium		Bronchospasm
2003	1993	Levomethadyl		Fatal arrhythmia
2004	1999	Rofexocib	Pain relief	Heart attack; stroke
2005	2001	Valdecoxib	Pain relief	Skin reactions (SJS)
2005(2006)*		Natalizumab*		Brain infection
2005	2004	99m Tc**	Diagnostic aid	Cardiopulmonary arrest
2005	1975	Pemoline	ADHD	Liver failure

* remarketed with restricted distribution ** Technetium (99m Tc) fanolesomab

Source: SM Huang

Mechanisms of Drug Interactions

- Pharmaceutical
  - Dosage form interactions
- **Pharmacokinetic**
  - Alterations in

Absorption, **D**istribution, **M**etabolism, **E**xcretion

Transporters **Phase I enzymes** **Phase II enzymes** **Transporters**

- Pharmacodynamic

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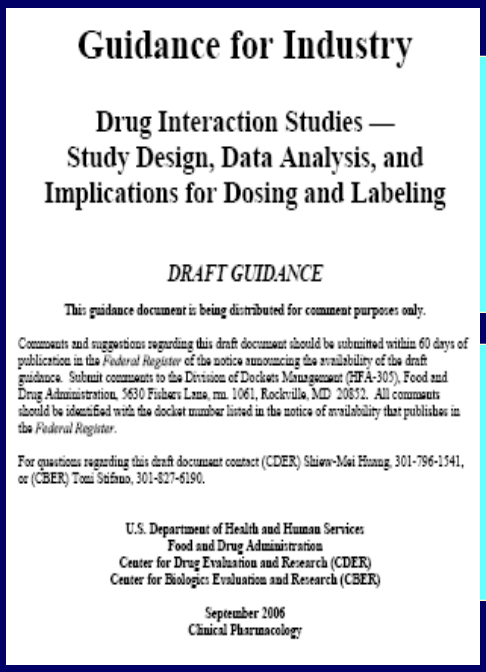


Guidance for Industry

Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Shiew-Mei Huang, 301-796-1541, or (CBER) Toni Stifano, 301-827-6190.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

September 2006
Clinical Pharmacology

Draft published for public comment September 11, 2006

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072101.pdf

FDA Drug Development & Drug Interaction website

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

Zhang L-7

- Metabolism, transport, drug-interaction info key to benefit/risk assessment

- Need exposure-response info to determine clinical significance

October 2006, advisory committee meeting:
http://www.fda.gov/ohrms/dockets/ac/cder06.html#PharmScience
http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4248s1-index.htm
<Huang, Temple, Throckmorton, Lesko, Clin. Pharmacol. Ther. Feb 2007>
<Huang, Strong, Zhang, Reynolds, Nallani, Temple, et al, J Clin Pharmacol, June, 2008>
<Zhang, Zhang, Strong, Reynolds, Huang, Xenobiotica, July 2008>

Zhang L-8

Highlights

CYP Enzymes

Major CYPs (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A)

- -specific substrates
- -specific inhibitors
- -inducers

In vitro and *in vivo*

Transporters

P-gp

- - specific substrates
- - general inhibitors
- - inducers

in vitro and *in vivo*

Others transporters:

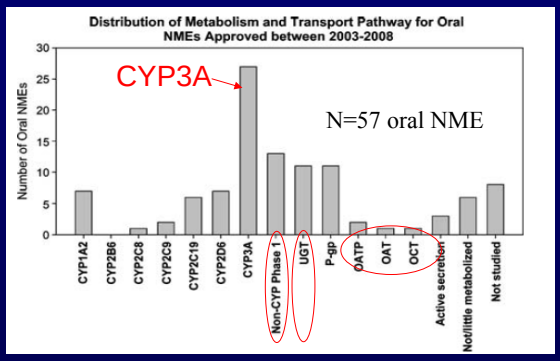
OATP, BCRP, OATs, OCTs, etc.

-general substrates, inhibitors, inducers (*in vitro/in vivo*)

On-going

Non-CYP-mediated DDI | Biologics DDI

A Recent Labeling Survey (New Molecular Entities Approved 2003-2008)



- 88% (57 out of 65) of NMEs intended for oral administration included *in vitro* study information for major metabolism and transport pathways.
- CYP3A is the main P450 enzyme involved in the metabolism of NMEs.
- Most NMEs were studied for their inhibition or induction potential for major P450 enzymes.
- *In vitro* evaluation studies are increasingly conducted with regard to whether an NME is a substrate or inhibitor for phase II enzymes (mostly UGTs) and transporters other than P-gp (e.g., BCRP, OATP1B1, OAT, and OCT).

Zhang L, et al, The AAPS Journal 2009; 11 (2): 300-306

Non-CYP Enzymes

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Non-CYP Phase I Enzymes

- Monoamine oxidase (MAO)
  - Dopamine
- Xanthine oxidase (XO)
  - Theophylline, allopurinol
- Alcohol/aldehyde dehydrogenase
  - Ethanol, methotrexate
- Flavin monooxygenase (FMO)

Drug Interaction involving MAO inhibitors (MAOIs)

- The MAOIs are infamous for their numerous drug interactions (food, over-the-counter and prescription medicines)
- Food:
  - MAO inhibitors (particularly MAOIs that inhibit the isozyme MAO-A) are known to interfere with the inactivation of tyramine found in various foods (e.g., cheese), leading to hypertensive crisis
    - Dietary restriction
- Drugs: MAO substrates and substances that increase serotonin, norepinephrine, and/or dopamine activity
  - MAOIs should not be combined with other psychoactive substances (antidepressants, painkillers, stimulants, etc.)
    - Class labeling of contraindication or warnings/precautions

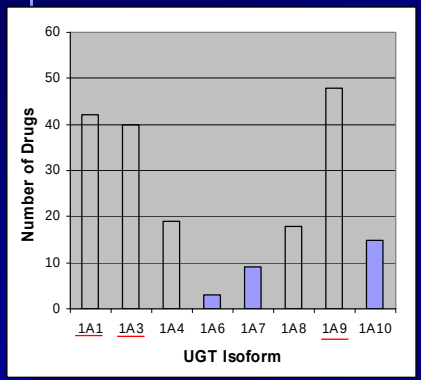
Phase II Enzymes

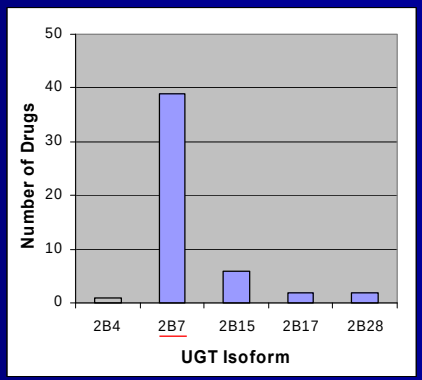
Reaction	Enzyme	Functional Group
Glucuronidation	UDP-Glucuronyltransferase	-OH, -COOH, -NH2, -SH
Glycosidation	UDP-Glycosyltransferase	-OH, -COOH, -SH
Sulfation	Sulfotransferase	- NH2,, -SO2NH2, -OH
Methylation	Methyltransferase	-OH, -NH2
Acetylation	Acetyltransferase	-NH2, -SO2NH2, -OH
Amino acid conjugation		-COOH
Glutathione conjugation	Glutathione-S-transferase	Epoxide, organic halide
Fatty acid conjugation		-OH
Condensation		Various

UGTs

- Important metabolizing enzymes
  - Responsible for ~35% of all drugs metabolized by phase II enzymes
  - Also metabolize endogenous substances, e.g., bilirubin
- Multiple isoforms
  - > 20 cloned
- Expressed in liver as well as extrahepatic tissues such as kidney, intestine, colon, lung, etc.
  - Liver: UGT1A1, 1A3, 1A4, 1A6, 1A9, 2B7, 2B15, etc.
  - Extrahepatic: UGT1A7, UGT1A8, UGT1A10, etc.

The distribution of UGT isoforms reported for glucuronidation of drugs





A) 192 for UGT1A

B) 51 for UGT2B

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Source: J Strong; Zhang Y. et. al. (book chapter submitted)

UGTs and Drug Interactions

- Like CYP enzymes, they are inhibitable and inducible and polymorphisms in UGTs lead to PK differences
- Unlike CYP enzymes, there is no consensus with respect to the in vitro tools, i.e., enzyme systems, selective substrates, inhibitors, or inducers for studying the UGT enzymes.
  - Lack of in vitro-in vivo correlation
- UGTs in general have broad and overlapping substrate selectivity
  - Some isoforms show low affinity and high capacity
  - Most inhibition < 3 fold
    - Clinical significance will depend on therapeutic window of the substrate drug
- Polymorphisms in UGTs can affect extent of drug interaction
- In lieu of lack of specific UGT inhibitors, PK studies stratified by various UGT genotypes may illustrate the importance of that particular UGT pathway in PK or PD.

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Selected Drugs that are UGT Substrates

UGT	Substrates
1A1	(SN38), ezetimibe, mycophenolic acid, raloxifene, raltegravir
1A3	Deferasirox, ketoprofen, ezetimibe
1A4	Lamotrigine, posaconazole
1A6	(SN38)
1A9	Diflunisal, fenofibrate, (SN-38), mycophenolic acid, R-oxazepam, retigabine, rotigotine
2B7	Gemfibrozil, lamotrigine, mycophenolic acid, morphine, R-oxazepam, zidovudine
2B15	Lorazepam, tolcapone, rotigotine

< Data from "Drugs @ FDA": http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>
< Kiang TKL, et al, Pharmacology & Therapeutics 2005: 106: 97-132>
< University of Washington Drug Interaction database>

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Selected Drugs that are UGT Inhibitors and Inducers

Inhibitors

-Decrease in CL up to 71%

- Atazanavir
- Probenecid*
- Valproate

Inducers

-Increase in CL up to 270%

- Rifampin
- Rifabutin
- Carbamazepine
- Phenytoin
- Oxcarbazepine
- Oral Contraceptives
- Ritonavir
- Nevirapine
- Methsuximide
- Phenobarbital

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Transporters

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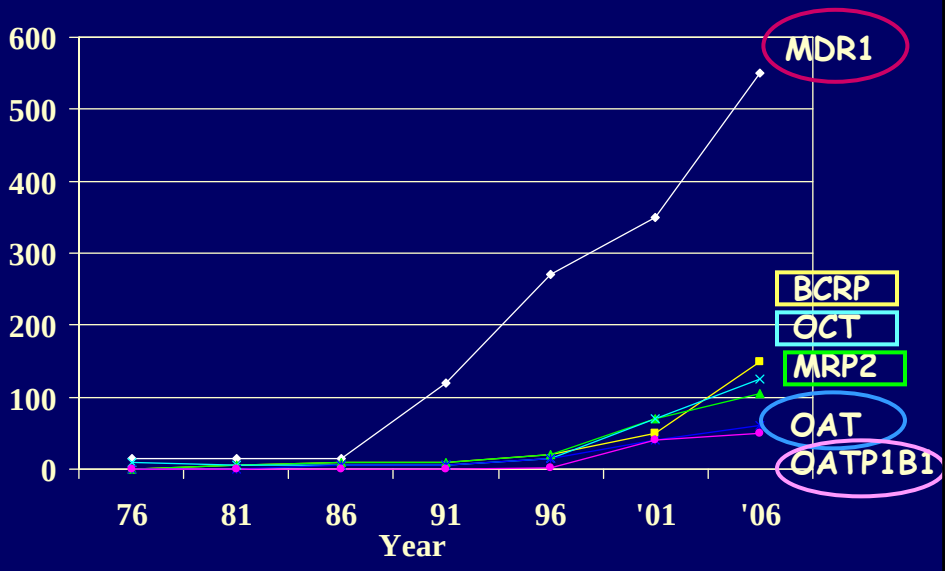
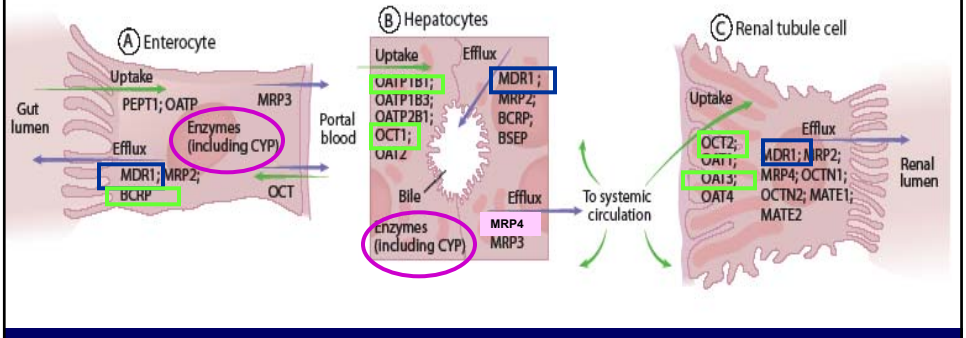
Number of published papers/patents



<Survey via Biovista; courtesy: Aris Persidis>
<http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4248s1-6-FDAHuang_files/frame.htm>

Zhang L-21

Selected efflux & uptake transporters in the gut wall (a), liver (b), and kidneys (c)



Huang S-M, Lesko LJ, and Temple R, "Adverse Drug Reactions and Pharmacokinetic Drug Interactions", Chapter 21, Adverse Drug Reactions and Drug Interactions in Part 4, FUNDAMENTAL PRINCIPLES: Clinical Pharmacology, "Pharmacology and Therapeutics: Principles to Practice," Ed. Waldman & Terzic, Elsevier, 2009 (ISBN: 978-1-4160-6098-7)

Zhang L-22

Complexities for Evaluation of Transporter-Mediated Drug Interactions

- Transporters are present in varying abundance in *ALL* tissues in the body
- Tissue-specific drug concentrations are determined by metabolism, uptake, and efflux transporters.
- Drug concentrations measured in plasma may not reflect levels in tissues.
- Redundant specificities among transporters within a particular tissue
  - Multiple transporters with overlapping substrate specificities will determine tissue specific drug concentrations.

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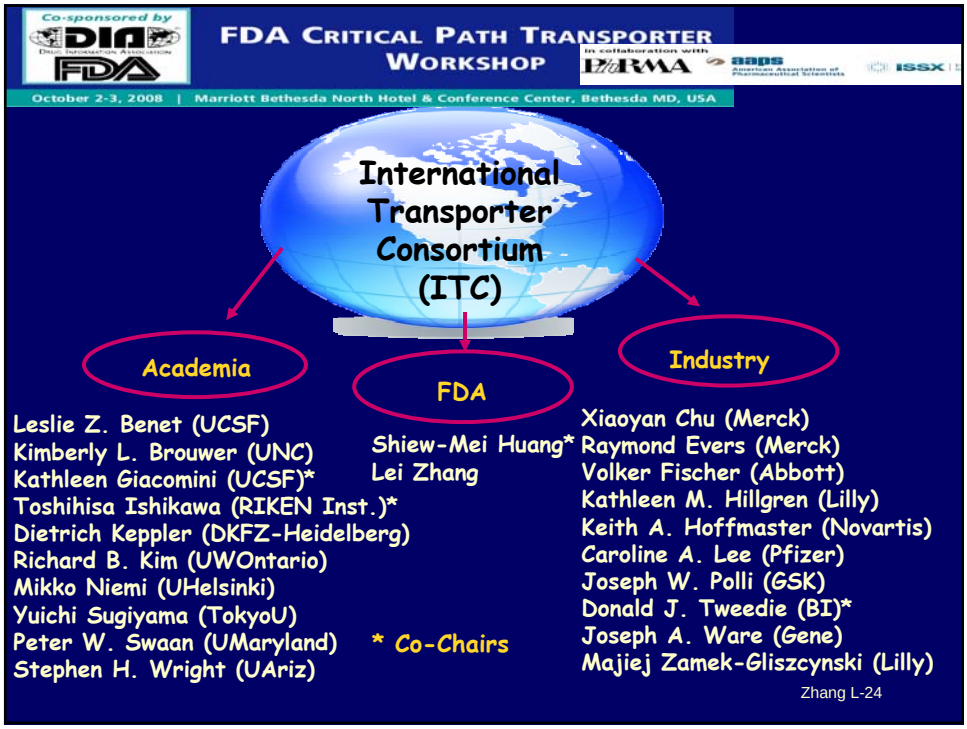

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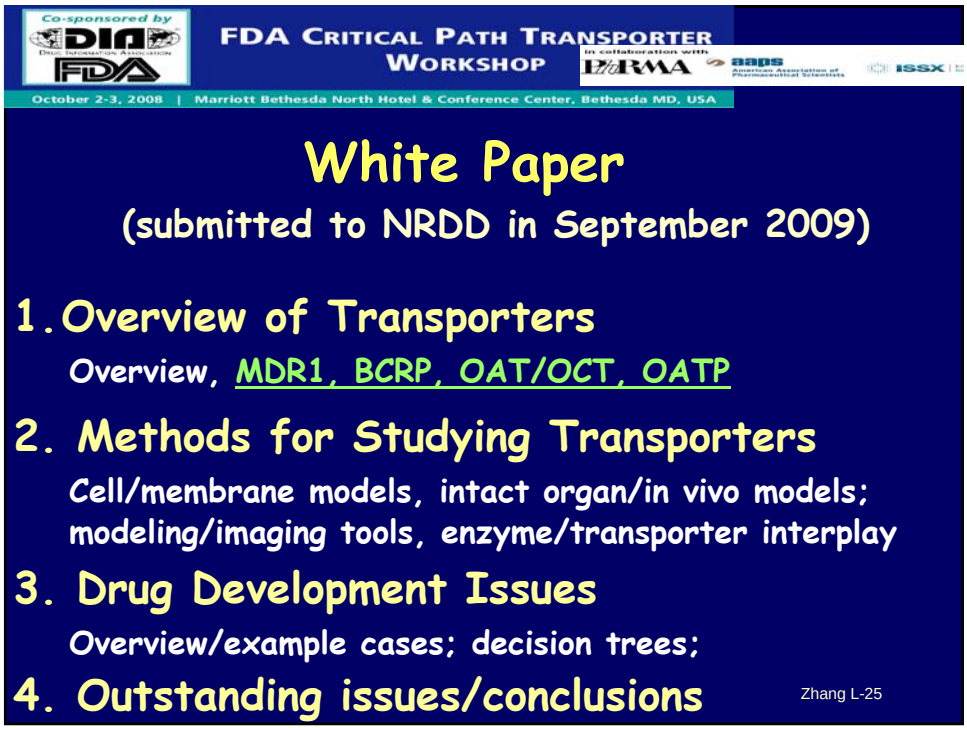

IND/NDA Discussions*

Transporter	Recommendations
No data on P-gp (oncology)	Post-marketing commitment as P-gp substrate or inhibitor
OATP1B1 substrate (HIV)	Recommended study with lopinavir/ritonavir
OATP1B1 inhibitor	Sponsor studied rosuvastatin
CYP3A/OATP1B1 inhibitor	Sponsor studied simvastatin

* Not an extensive list; case examples from recent Investigational New Drug/New Drug Application discussions- courtesy of Abraham S, Booth B, Zhang L, Zhang YD

Zhang L-26

<SM Huang, DIA/FDA Critical Path Transporter Workshop>

Transporter Information in the Drug Labeling

Transporter	Drug Names*
P-gp	Aliskiren, ambrisentan, [aprepitant], *clarithromycin*, colchicine, [dexvenafaxine], *dronedarone*, [eltrombopag], ***everolimus***, fexofenadine, [fosaprepitant], [ixabepilone], ***lapatinib***, ***maraviroc***, ***nilotinib***, *paliperidone*, posaconazole, [prasugrel], [[propafenone]], propranolol, ***ranolazine***, saxagliptin, silodosin, sirolimus, sitagliptin, ***tipranavir*****, ***tolvaptan***, topotecan, [vorinostat]
OATP1B1	Atorvastatin, *cyclospoprine*, *eltrombopag****, *lapatinib*, valsartan
OATP	Ambrisentan
OAT	Sitagliptin (OAT3)
OCT	Metformin, pramipexole, [saxagliptin], [sitagliptin], varenicline (OCT2)
BCRP	Lapatinib, topotecan
MRP	Mycophenolate (MRP2), [ixabepilone] (MRP1),valsartan (MRP2)

*Not an extensive list: data based on a preliminary survey of electronic PDR and Drugs@FDA on September 18, 2009. They are substrates, *inhibitors*, (***both substrates and inhibitors***), [not a substrate or an inhibitor] or [[not studies as a substrate or an inhibitor]]; **:Tipranavir is also a P-gp inducer *** an inhibitor; its labeling contains a list of OATP1B1 substrates

Zhang L-27

<Huang, SM, Zhang L, Giacomini KM, Clin Pharmacol Ther (in press)>

New Drug Application (NDA) and Labeling Examples

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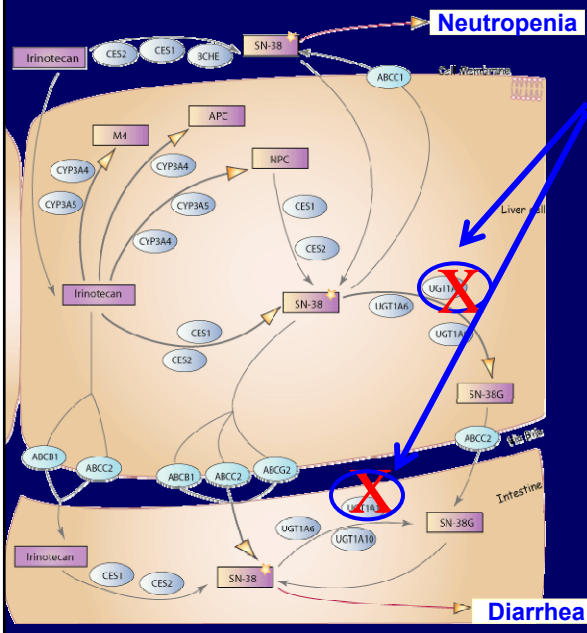
Irinotecan (Camptosar®)



The UGT1A1*28 allele is common (30%) in Caucasians and is associated with a significant decrease in UGT1A1 activity.

Carriers of UGT1A1*28 when treated with irinotecan can experience AEs

Zhang L-29

<http://www.pharmgkb.org/search/pathway/irinotecan/liver.jsp>

CAMPTOSAR (irinotecan) [Dosage & Administration]
When administered in combination with other agents, or as a single-agent, a reduction in the starting dose by at least one level of CAMPTOSAR should be considered for patients known to be homozygous for the UGT1A1*28 allele (See CLINICAL PHARMACOLOGY and WARNINGS).

FDA NEWS

THE FOOD AND DRUG ADMINISTRATION / AN AGENCY OF THE U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICE

FOR IMMEDIATE RELEASE
P05-53
August 22, 2005

Media Inquiries: Julie Zawisza
301-827-6242
Consumer Inquiries: 888-INFO-FDA

FDA CLEARS GENETIC TEST THAT ADVANCES PERSONALIZED MEDICINE
Test Helps Determine Safety of Drug Therapy

Today, FDA cleared for marketing a new blood test that will help doctors make personalized drug treatment decisions for some patients. The Invader UGT1A1 Molecular Assay detects variations in a gene that affects how certain drugs are broken down and cleared by the body. Doctors can use this information to help determine the right drug dosage for individual patients, and minimize harmful drug reactions.

"This test represents the power of DNA-based testing to provide individualized medical care," said Daniel Schultz, MD, Director of FDA's Center for Devices and Radiological Health. "These technologies can significantly improve patient management and reduce the risk of ineffective or even harmful drug therapy by telling doctors how to individualize drug dosing."

Zhang L-30

< http://www.fda.gov/cder/foi/label/2005/020571s024,027,028lbl.pdf >

'Irinogenetics: How Many Stars Are There in the Sky?"

J. Clin. Oncology 27:2604-14, 2009

Comprehensive Pharmacogenetic Analysis of Irinotecan Neutropenia and Pharmacokinetics

Federico Innocenti, Deanna L. Kroetz, Erin Schuetz, M. Eileen Dolan, Jacqueline Ramírez, Mary Relling, Peixian Chen, Soma Das, Gary L. Rosner, and Mark J. Ratain

- Variations in ABCB1, ABCC1, ABCC2, SLCO1B1, HNF1A, and UGT1A1 correlated with irinotecan and SN-38 exposure, explaining 30%-40% of the variations among individuals.

Zhang L-31

Beyond UGT1A1*28

-Irinotecan PK and Neutropenia-

Multiple factors: UGT1A1*93, ABCB1, ABCC1, ABCC2, SLCO1B1, Sex, etc…

→Would a composite pharmacogenetic test be more predictive than UGT1A1 alone?

→ Important transporter-based interactions?

Innocenti et al, J. Clin. Oncology 27:2604-14, 2009

Zhang L-32

Raltegravir Labeling
-UGT1A1 Inhibition/Induction-

7.2 Effect of Other Agents on the Pharmacokinetics of Raltegravir

- "Raltegravir is not a substrate of cytochrome P450 (CYP) enzymes. Based on in vivo and in vitro studies, raltegravir is eliminated mainly by metabolism via a UGT1A1-mediated glucuronidation pathway."
- "Rifampin, a strong inducer of UGT1A1, reduces plasma concentrations of ISENTRESS. Therefore, the dose of ISENTRESS should be increased during coadministration with rifampin [see Dosage and Administration (2)]. The impact of other inducers of drug metabolizing enzymes, such as phenytoin and phenobarbital, on UGT1A1 is unknown."
- "Coadministration of ISENTRESS with drugs that inhibit UGT1A1 may increase plasma levels of raltegravir."

Zhang L-33

Raltegravir Labeling
-UGT1A1 Polymorphism-

12.3 Pharmacokinetics

UGT1A1 Polymorphism

- "There is no evidence that common UGT1A1 polymorphisms alter raltegravir pharmacokinetics to a clinically meaningful extent. In a comparison of 30 subjects with *28/*28 genotype (associated with reduced activity of UGT1A1) to 27 subjects with wild-type genotype, the geometric mean ratio (90% CI) of AUC was 1.41 (0.96, 2.09)."

July 2009 raltegravir (ISENTRESS) label
<http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022145s004lbl.pdf>

Zhang L-34

Atazanavir Labeling -UGT1A1 inhibition-

- WARNINGS-Drug Interactions

Atazanavir is an inhibitor of CYP3A, CYP2C8, and UGT1A1. Coadministration of REYATAZ and drugs primarily metabolized by CYP3A [eg, calcium channel blockers, HMG-CoA reductase inhibitors, immunosuppressants, and phosphodiesterase (PDE5) inhibitors], CYP2C8, or UGT1A1 (eg, irinotecan) may result in increased plasma concentrations of the other drug that could increase or prolong its therapeutic and adverse effects.

February 2008 atazanavir (REYATAZ) label
<http://www.fda.gov/cder/foi/label/2008/021567s018lbl.pdf>

Pitavastatin -OATP-

- 7th Statin approved in the U.S. in Aug 2009
  - 6th on the market
- Metabolized by glucuronidation via UGTs (major), CYP2C9, 2C8 (minor), etc.
- A substrate for OATP1B1 (major), OATP1B3, and BCRP
- Like other statins, show dose/exposure-related myopathy side effects.
- Inhibition of OATP would be a concern.

<Hirano et al , Drug Metab Dispos. 34(7):1229-36m 2006,>
<Deng et al, Pharmacogenet Genomics. 18(5):424-33, 2008>

Cyclosporine and Pitavastatin

Table 2. Effect of Co-Administered Drugs on Pitavastatin Systemic Exposure

Co-administered drug	Dose regimen	Change in AUC*	Change in C_{max*}
Cyclosporine	Pitavastatin 2 mg QD for 6 days + cyclosporine 2 mg/kg on Day 6	↑ 4.6 fold†	↑ 6.6 fold †

→ Based on exposure-safety response analysis, cyclosporine is contraindicated with pitavastatin.

<http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022363s000lbl.pdf>

Effect of Other Drugs on PK of Pitavastatin

Table 2. Effect of Co-Administered Drugs on Pitavastatin Systemic Exposure

Co-administered drug	Dose regimen	Change in AUC*	Change in C_{max*}
Cyclosporine	Pitavastatin 2 mg QD for 6 days + cyclosporine 2 mg/kg on Day 6	↑ 4.6 fold†	↑ 6.6 fold †
Erythromycin	Pitavastatin 4 mg single dose on Day 4 + erythromycin 500 mg 4 times daily for 6 days	↑ 2.8 fold †	↑ 3.6 fold †
Rifampin	Pitavastatin 4 mg QD + rifampin 600 mg QD for 5 days	↑ 29%	↑ 2.0 fold
Atazanavir	Pitavastatin 4 mg QD + atazanavir 300 mg daily for 5 days	↑ 31%	↑ 60%
Gemfibrozil	Pitavastatin 4 mg QD + gemfibrozil 600 mg BID for 7 days	↑ 45%	↑ 31%

<http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022363s000lbl.pdf>

OATP1B1 inhibitors

- √ Cyclosporine
- √ Gemfibrozil and gemfibrozil-O-glucoronide
- √ Rifampin
- √ Clarithromycin, erythromyzcin, roxithromycin, telithromycin
- → Indinavir, ritonavir, saquinavir

<M Niemi, DIA/FDA critical path transporter workshop 2008>

Post-Marketing Requirement for Pitavastatin

- A drug-drug interaction clinical trial to examine the effect of the combination of lopinavir/ritonavir on pitavastatin C_{max} and AUC.
- Projected report submission date: December 31, 2010

<http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2009/022363s000ltr.pdf>

Pitavastatin Labeling

7.2 Lopinavir/Ritonavir

Based on data with another HMG-CoA reductase inhibitor that has a similar pharmacokinetic profile to that of pitavastatin, **coadministration of the protease inhibitor combination, lopinavir/ritonavir, with LIVALO may significantly increase pitavastatin exposure. Therefore, LIVALO should not be used with this combination of protease inhibitors.** [*see Limitations of Use (1.2)*].

<http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022363s000lbl.pdf>

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Summary (1)

- CYP-based interactions well defined in general; labeling recommendations based on clinical significance: exposure-response relationship & benefit/risk ratio
- Unlike CYP enzymes, there is no consensus with respect to the tools and criteria for studying the non-CYP enzymes for drug interaction evaluation and prediction.
  - -On a case-by-case basis
  - -Prior knowledge of the drug class, therapeutic range
  - -Therapeutic area and concomitant medications

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Summary (2)

- Phase II metabolism information has been increasingly included in the drug label (some with genotype-guided dosing).
- If an NME is predominantly eliminated via glucuronidation, the sponsor needs to consider identifying specific UGT enzymes with recombinant human UGTs, many available from commercial sources.

Summary (3)

- Transporter-based interactions have been increasingly evaluated; results have been included in the drug label
  - P-gp based interactions are among the most evaluated
  - Other transporters (e.g., OATP, OCT, OAT, BCRP) are also evaluated based on therapeutic area drug class.

* Study design issues need to be addressed (e.g., probe substrates, inhibitors)

- Post-marketing studies may be required if lack of non-CYP enzyme or transporter information would impact clinical safety/efficacy.

Summary (4)

- Drug Interaction Guidance is being revised

- Efforts in development/evaluation of models predicting the extent of drug interactions ongoing at the FDA

  * *in vitro* to *in vivo*
  * single pair to multiple interactions
    - multiple CYP inhibitors
    - multiple modulators (CYP/transporter inhibition/induction)
    - effect of non-CYP metabolizing enzymes
    - effect of genetics

Drug Interactions Working Group and *ad hoc* Members

Sophia Abraham
Sang Chung
Shiew-Mei Huang
Patrick Marroum
Nam Atik Rahman
Sally Yasuda

Sayed Al-Habet
Philip Colangelo
Ron Kavanagh
Srikanth Nallani
Kellie Reynolds
Lei K Zhang

Raman Baweja
Paul Hepp
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Thank you!

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Abbreviation List

- P-gp: P-glycoprotein
- MDR: Multidrug Resistance
- BCRP: Breast Cancer Resistant Protein
- OAT: Organic Anion Transporter
- OCT: Organic Cation Transporter
- OATP: Organic Anion Transporting Polypeptide

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